
MMFF VII. Characterization of MMFF94, MMFF94s, and Other Widely Available Force Fields for Conformational Energies and for Intermolecular-Interaction Energies and Geometries

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ABSTRACT: This article provides extensive comparisons for the MMFF94, MMFF94s, CFF95, CVFF, MSI CHARMM, AMBER*, OPLS*, MM2*, and MM3* force fields to experimental and high-quality *ab initio* data for conformational energies and to scaled *ab initio* data for hydrogen-bonded complexes. Some comparisons are also presented for CHARMM 22. The tests of conformational energies consisted of two sets of comparisons to experiment and one more extensive set of comparisons to relatively high-quality *ab initio* data. As in the derivation of MMFF94, scaled HF/6-31G* energies and geometries were used to assess the reasonableness of the calculated intermolecular interaction energies and geometries. The comparisons for intermolecular interactions appear to be the first broadly based comparisons to appear in the chemical literature. Taken together, the comparisons reveal that most of the force fields make sizable errors and frequently produce qualitatively incorrect results for both conformational and intermolecular-interaction energies. For example, three of the force fields produce individual errors in conformational energy of more than 10 kcal/mol, and four rate thiophene as a stronger hydrogen-bond acceptor than ammonia. Only MMFF94 and MMFF94s perform consistently well. Some MMFF deficiencies are apparent, however, particularly for conformational energies of

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halocyclohexanes. These deficiencies, and others recently found for condensed-phase simulations, will need to be addressed in any future reparameterization of MMFF. The quantum-chemical data used in this work have been placed on the Computational Chemistry List web site. © 1999 John Wiley & Sons, Inc. J Comput Chem 20: 730–748, 1999

Keywords: force field; conformational energy; intermolecular interactions; hydrogen bonding; scaled quantum mechanics

Introduction

This article, the seventh in a series,^{1–6} examines the ability of MMFF94, MMFF94s, and seven other widely used force fields to reproduce experimental and theoretical values for conformational energies and to produce realistic values and trends for intermolecular-interaction energies and geometries in hydrogen-bonded complexes. Accurate conformational and intermolecular-interaction energies are key determinants of success in molecular modeling studies that range from pharmacophoric hypothesis generation and testing to prediction and rationalization of ligand binding affinities. In addition to MMFF94 and MMFF94s, we examine CFF95⁷ and CVFF⁸ (accessed⁹ through Version 3.0 of Cerius²); the MSI CHARMM force field (accessed⁹ through QUANTA 97); and the AMBER*, OPLS*, MM2*, and MM3* force fields (accessed through Version 5.5 of BatchMin¹⁰). We excluded the UFF¹¹ and Dreiding¹² force fields (available through Cerius²) and the Tripos¹³ force field (available through SYBYL¹³), which were each developed for use without charges, as being unsuitable for use in studies involving intermolecular interactions. The last three force fields were previously examined for conformational energies by Gundertofte et al.,¹⁴ who also tested UFF with QEq charges¹⁵ and found its uncertain performance to be further degraded. We include CVFF, however, even though it did not perform well in Gundertofte et al.'s study,¹⁴ because it is widely used in studies involving intermolecular interactions but appears to not have been previously characterized for general applications involving such interactions.

Among other widely used force fields, we did not have access to MM2,¹⁶ MM3,¹⁷ MM4,¹⁸ AMBER 3,¹⁹ AMBER 4,²⁰ GROMOS,²¹ or the recently developed OPLS-AA²² (all-atom) force fields. We did have access to AMBER94, the BatchMin implementation of AMBER 4, but omitted it because it

could handle very few of the systems considered. AMBER 4 and GROMOS may not have been appropriate choices in any event, because their published parameterizations are too limited to cover the range of chemical structures examined here.

Most comparisons made in this article confer an advantage on MMFF94 and MMFF94s because they use reference data closely related to data used in their derivation. To level the playing field somewhat, we added to the 37 experimental conformational energy comparisons previously used in MMFF's characterization⁴ another 19 experimental comparisons that were employed by Gundertofte et al.¹⁴ but for which no related *ab initio* data were used in deriving MMFF94. But while MMFF retains an advantage, we stress that the systems considered are realistic ones and that large errors made by any of the force fields must be regarded as giving serious cause for concern.

Comparisons to Experiment for Conformational Energies

Table I presents detailed results for the 37 comparisons to experiment previously used in characterizing MMFF94⁴ (set 1); Table II (set 2) gives results for the 19 just-cited comparisons to experiment considered by Gundertofte et al.,¹⁴ whose full study included many of the comparisons found in Table I. All calculations used cutoff distances for nonbonded interactions that exceeded the largest intramolecular dimension encountered, and all employed a constant dielectric of 1.0. The reader should note that the present results for AMBER*, MM2*, and MM3* differ from those of Gundertofte et al.,¹⁴ who used the then-current BatchMin default of a distance-dependent (1r) dielectric. Here we examine whether the relatively good performances these workers reported for MM2* and MM3* can also be obtained when the new BatchMin default choice of a unit constant dielectric is utilized.

TABLE I.
Comparison of Experimental and Force-Field^a Conformational Energies (Set 1; kcal / mol).

Conf. Comparison	Expt. ^b	MMFF 94s	MMFF 94	CFF 95	CVFF	MSI CHARMm	AMBER*	OPLS*	MM2*	MM3*
<i>N</i> -Methylformamide, <i>c</i> – <i>t</i>	1.4 (C)	1.09	1.27	1.83	<u>–4.71</u>	3.44	1.57	0.41	0.46	1.50
<i>N</i> -Methylacetamide, <i>c</i> – <i>t</i>	2.3 (C)	1.96	2.18	3.09	<u>0.96</u>	2.46	2.33	1.98	1.75	2.31
Formic acid, <i>trans</i> – <i>cis</i>	3.90 (D)	4.89	4.89	4.48	6.93	5.97	6.56	7.64	11.37	4.89
Glyoxylic acid, [O=CC=O <i>t</i> , O=COH <i>c</i>] – [O=CC=O, <i>t</i> , O=COH <i>t</i>]	1.2 (D)	1.91	1.91	2.94	<u>0.22</u>	0.89	1.07	<u>5.08</u>	<u>–5.68</u>	<u>–0.49</u>
Methyl formate, <i>trans</i> – <i>cis</i>	4.75 (B)	5.28	5.28	5.09	1.27	5.54	1.34	0.87	5.61	2.18
Methyl acetate, <i>trans</i> – <i>cis</i>	8.5 (D)	8.27	8.27	8.67	<u>7.85</u>	9.09	<u>7.42</u>	<u>7.47</u>	6.68	7.85
Ethyl formate, [O=COC <i>c</i> , COCC <i>g</i>] – [O=COC <i>c</i> , COCC <i>a</i>]	0.19 (D)	0.44	0.44	0.67	1.91	—	0.99	0.69	0.27	0.23
Propionaldehyde, <i>skew</i> – <i>cis</i>	0.67 (A)	0.53	0.53	1.09	—	0.32	1.65	–0.46	0.91	1.11
2-Butanone, <i>skew</i> – <i>cis</i>	1.07 (C)	0.83	0.83	1.35	—	0.19	1.73	–0.04	1.57	1.61
1,3-Butadiene, <i>g</i> – <i>s-trans</i>	2.89 (A)	2.47	2.47	3.39	4.38	2.39	2.45	2.80	2.74	1.72
2-Methyl-1,3-butadiene, <i>gauche</i> – <i>s-trans</i>	2.65 (A)	2.12	2.12	2.79	1.39	1.95	3.29	1.85	2.50	1.63
Acrolein, <i>cis</i> – <i>trans</i>	1.70 (B)	2.04	2.04	1.59	1.76	2.47	2.03	1.69	1.64	1.98
1,2-Difluoroethane, <i>a</i> – <i>g</i>	0.56 (B)	0.63	0.63	<u>–1.57</u>	<u>–3.56</u>	1.05	<u>–1.16</u>	–0.93	0.01	0.05
1,2-Dichloroethane, <i>g</i> – <i>a</i>	1.08 (B)	1.24	1.24	1.22	2.77	1.47	1.13	0.87	1.13	1.95
1-Fluoropropane, <i>a</i> – <i>g</i>	0.35 (A)	0.05	0.05	–0.93	<u>–1.67</u>	–0.12	0.03	–0.41	–0.08	–0.10
1-Chloropropane, <i>a</i> – <i>g</i>	0.09 (A)	0.01	0.01	–1.03	<u>–1.49</u>	–0.15	–0.07	–0.39	–0.23	–0.29
2-Methoxytetrahydropyran, [OCOMe <i>g</i> , OMe eq] – [OCOMe <i>g</i> , OMe ax]	1.05 (C)	1.81	1.81	1.88	<u>–0.77</u>	2.37	0.97	1.70	2.26	1.62
2,5-Dimethyl-1,3-dioxane, [2 eq, 5 ax] – [2 eq, 5 eq]	0.92 (C)	0.50	0.50	0.04	2.35	<u>–0.65</u>	<u>–0.68</u>	0.41	0.69	0.76
Isopropylamine, lpNCH <i>gauche</i> – <i>anti</i>	0.45 (B)	0.45	0.45	0.16	–0.49	–0.07	0.24	0.00	0.15	0.22
Cyclohexylamine, ax – eq	1.15 (E)	0.67	0.67	0.83	4.49	1.78	<u>–0.74</u>	0.62	1.38	1.23
Piperidine, ax – eq	0.53 (B)	0.90	0.90	0.05	–0.69	0.13	0.14	–0.04	0.30	0.31
<i>N</i> -Methylpiperidine, ax – eq	3.15 (D)	3.29	3.29	3.25	1.35	2.70	1.26	2.32	2.53	2.30
Ethanol, <i>gauche</i> – <i>anti</i>	0.12 (D)	0.18	0.18	0.37	<u>–1.44</u>	0.23	0.36	0.00	0.60	0.41
Isopropanol, HCOH <i>a</i> – <i>g</i>	0.28 (D)	0.17	0.17	0.40	–1.07	0.02	0.24	0.00	0.62	0.68
Cyclohexanol, ax C ₁ – eq C ₁	0.58 (C)	0.32	0.32	0.24	–0.75	0.40	–0.58	0.50	0.59	0.74
Methyl ethyl ether, <i>g</i> – <i>a</i>	1.5 (B)	1.50	1.50	1.46	1.49	1.53	1.80	1.85	1.74	1.48
Methyl vinyl ether, C=COC <i>skew</i> – <i>cis</i>	1.70 (B)	2.22	2.22	<u>–3.10</u>	—	2.10	<u>–2.90</u>	<u>–3.94</u>	1.07	0.60
Diethyl ether, [CCOC <i>a</i> , COCC <i>g</i>] – [CCOC <i>a</i> , COCC <i>a</i>]	1.14 (C)	1.52	1.52	1.37	1.39	1.55	1.83	1.84	1.77	1.49
Methoxycyclohexane, ax C ₁ – eq C ₁	0.55 (F)	0.42	0.42	–0.11	2.71	0.70	–0.34	0.37	0.56	0.76
Butane, <i>gauche</i> – <i>anti</i>	0.67 (B)	0.79	0.79	0.89	1.66	0.78	0.38	0.95	0.86	0.81
Cyclohexane, twist boat – chair	5.5 (C)	5.93	5.93	7.08	<u>10.60</u>	6.72	5.79	6.77	5.36	5.76
Methylcyclohexane, ax – eq	1.75 (C)	1.37	1.37	1.84	3.04	1.80	0.90	1.78	1.78	1.77
2,3-Dimethylbutane, HC ₂ C ₃ H <i>gauche</i> – <i>anti</i>	0.05 (B)	–0.23	–0.23	0.13	–0.10	0.40	–0.22	–0.48	0.15	0.38

TABLE I.
(Continued)

Conf. Comparison	Expt. ^b	MMFF 94s	MMFF 94	CFF 95	CVFF	MSI CHARMm	AMBER*	OPLS*	MM2*	MM3*
Cyclooctane, $D_{4d} - C_s$ boat chair	1.9 (C)	1.44	1.44	1.21	−3.20	0.45	0.84	−1.67	0.97	1.11
Cyclononane, [255] $C_2 - [333] D_3$	1.0 (C)	1.22	1.22	1.63	−1.63	1.12	1.07	0.80	0.75	0.84
1-Butene, <i>cis</i> – <i>skew</i>	0.22 (C)	0.26	0.26	0.72	0.00	0.46	0.66	1.00	0.49	0.68
2-Butene, <i>cis</i> – <i>trans</i>	1.2 (B)	1.35	1.35	1.43	1.90	1.61	1.55	2.49	1.44	1.02

^a Force-field values in boldface differ from experiment by > 1.5 kcal/mol; values in bold underline differ by > 3.0 kcal/mol. All calculations used a constant dielectric of 1.0 and included all nonbonded interactions (no cutoffs).

^b Measurement: A, difference between potential energy minima along a 1-dimensional torsional coordinate, gas phase; B, ΔH , gas phase; C, ΔH , liquid phase or solution; D, ΔG , gas phase; E, ΔG , liquid phase or solution; F, ΔG , solution, low temp. For literature citations, see Table A.I of Appendix A (Supplementary Material).²³

EXPERIMENTAL CONFORMATIONAL ENERGIES

Experimental determinations of conformational energy are typically made under a wide variety of disparate conditions. Thus, most experimental determinations represent differences in enthalpy measured in the gas phase or in solution. Still others, however, are relative free energies in solution. For only a few of the systems (those denoted in Table A-I of Appendix A, Supplementary Material,²³ as ΔH_{gp}^0) do the experimental measurements correspond reasonably directly to the calculated force-field quantity (i.e., to the energy difference between two potential minima).

References for set 1 are given in Table A-I of the appendix, which reports experimental values and their assigned uncertainties, where the latter are reported or can be ascertained. This table also specifies the type of quantity measured and the method used. This information is summarized in Table I for set 1 and is indicated in Table II for set 2 using a one-letter code closely related to the code employed by Gundertofte et al.¹⁴ In a number of cases, Table A.I specifies alternative experimental values (the first of which is always the one used in the present comparisons). These instances sometimes mark cases in which, for reasons specified in the appendix, we chose to use an experimental value in this work that is different from the one we used previously.⁴ For set 2 we adopted the experimental values cited by Gundertofte and colleagues¹⁴ without further examination. References for set 2 may be found in the Gundertofte et al. article.¹⁴

COMPARISON OF THEORETICAL CALCULATIONS TO EXPERIMENT

Because the experimental determinations are so diverse, comparisons of theory to experiment should be viewed with caution. Taken in an overall sense, however, the data in Table III strongly suggest that experimental conformational energies provide relevant measures against which to judge the accuracy of force-field calculations. The table displays calculated conformational energies for seven levels of theory:

- HF/6-31G* at HF/6-31G*-optimized geometries;
- MP2/6-31G* at MP2/6-31G*-optimized geometries;
- MP2/TZP²⁴ at MP2/6-31G*-optimized geometries;
- “MP4SDQ/TZP,” which adds MP3 and MP4SDQ perturbative corrections²⁵ obtained with a modified²⁶ 6-31G* basis set²⁷ to the MP2/TZP results;
- LMP2/cc-pVTZ(-f), the computationally efficient localized MP2 method implemented by Friesner and coworkers²⁸;
- “LMP4/cc-pVTZ(-f),” a hybrid set obtained by adding the small-basis MP3 and MP4SDQ corrections⁴ to the latter; and
- GVB-LMP2/cc-pVTZ(-f), the Friesner group’s correlated multireference method.²⁸

The last of these is the best theoretical method we considered: it combines a high degree of electron correlation with a correlation-consistent cc-pVTZ

TABLE II. Comparison of Experimental and Force-Field^a Conformational Energies (Set 2; kcal / mol).

Conf. Comparison	Expt. ^b	MMFF 94 / 94s	CFF 95	CVFF	MSI CHARMm	AMBER*	OPLS*	MM2*	MM3*
1,3,5-Trineopentyl-2,4,5-tri-bromobenzene, twosym – allsym	1.04 (F)	2.07	0.94	1.45	0.64	0.75	1.45	1.85	1.62
Phenylcyclohexane, ax – eq	2.87 (F)	2.99	4.17	4.57	3.28	3.62	3.74	4.74	5.14
1,3-Dichloropropane, g, a – g, g	1.1 (B)	0.39	–0.92	–0.40	–0.24	–0.15	–0.43	0.50	0.18
1,3-Dichloropropane, a, a – g, g	1.5 (B)	1.13	–1.87	–0.44	–0.16	0.11	–0.56	1.45	0.60
Fluorocyclohexane, ax – eq	0.16 (B)	–0.37	1.63	2.82	0.36	0.17	0.80	0.15	0.22
Chlorocyclohexane, ax – eq	0.5 (B)	–0.35	1.72	2.47	0.53	0.32	0.70	0.42	0.58
Bromocyclohexane, ax – eq	0.7 (B)	–0.01	2.07	2.56	0.32	0.72	1.20	0.46	0.65
trans-1,2-Difluorocyclohexane, ax, ax – eq, eq	0.59 (C)	–0.22	1.67	1.78	0.77	–0.91	0.59	0.16	0.21
trans-1,2-Dichlorocyclohexane, eq, eq – ax, ax	0.93 (B)	2.20	–2.23	–1.85	0.94	0.61	–0.44	–0.32	0.91
trans-1,2-Dibromocyclohexane, eq, eq – ax, ax	1.5 (C)	1.69	–1.66	–2.24	2.29	–0.19	–1.41	1.07	0.80
trans-1,4-Difluorocyclohexane, eq, eq – ax, ax	1.14 (E)	2.59	–2.74	–3.78	1.02	0.94	–0.71	0.98	0.78
trans-1,4-Dichlorocyclohexane, eq, eq – ax, ax	0.8 (C)	2.01	–3.44	–3.37	–0.09	0.77	–0.37	0.05	–0.28
trans-1,4-Dibromocyclohexane, eq, eq – ax, ax	0.88 (C)	0.80	–3.13	–3.88	–0.41	0.51	–1.78	–0.34	–0.66
2-Methylpiperidine, NH eq, methyl ax – eq	2.5 (E)	2.38	2.45	2.45	2.36	1.22	2.06	2.13	2.34
3-Methylpiperidine, NH eq, methyl ax – eq	1.6 (E)	1.09	1.40	3.72	1.36	–0.01	1.21	1.62	1.48
4-Methylpiperidine, NH eq, methyl ax – eq	1.93 (E)	1.37	1.76	2.37	2.15	1.23	1.73	1.74	1.73
N,N-Dimethylcyclohexane, ax C _s – eq C ₁	1.31 (E)	0.80	1.02	7.08	2.14	0.70	1.90	0.99	1.18
trans-1,2-Dimethylcyclohexane, ax, ax – eq, eq	2.58 (E)	1.80	2.67	3.98	2.70	1.19	2.11	2.44	2.57
cis-1,3-Dimethylcyclohexane, eq, eq – ax, ax	5.5 (B)	5.08	5.39	7.52	4.87	4.19	5.43	5.34	5.70

^a Force-field values in boldface differ from experiment by > 1.5 kcal / mol; bold underline values differ by > 3.0 kcal / mol. All calculations used a constant dielectric of 1.0 and included all nonbonded interactions (no cutoffs).
^b Measurement: A, difference between potential energy minima along a 1-dimensional torsional coordinate, gas phase; B, ΔH , gas phase; C, ΔH , liquid phase or solution; D, ΔG , gas phase; E, ΔG , liquid phase or solution; F, ΔG , solution, low temp. For literature citations, see ref. 14.

(-f) basis set²⁹ that is larger and more flexible than the TZP basis set used in our earlier work. The *ab initio* calculations for the last six of these methods used MP2(FULL)/6-31G*-optimized geometries. All calculations were performed in these laboratories.^{4, 30}

Table IV shows that the *ab initio* relative energies increasingly closely reproduce the experimental values as higher levels of theory are employed.

Conversely, the simpler methods suffer a greater number of cases in which the theoretical and experimental conformational energies differ by at least 0.5 kcal/mol (shown in boldface in Table III) or by 1.0 kcal/mol or greater (shown in underlined boldface). The root mean square deviation (RMSD) for the best theoretical model (GVB-LMP2 with the correlation-consistent basis set) is 0.32 kcal/mol. This figure is probably about as close to

TABLE III.
Comparison of Experimental and *Ab Initio*^a Conformational Energies (Set 1; kcal / mol).

Conf. Comparison	Expt. ^b	Delta	HF / 6-31G*	MP2 / 6-31G*	MP2 / TZP	"MP4 / TZP"	LMP2 ^c	"LMP4" ^c	GVB- LMP2 ^c
<i>N</i> -Methylformamide, <i>c</i> – <i>t</i>	1.4	?	1.05	1.29	1.11	1.04	1.12	1.05	1.06
<i>N</i> -Methylacetamide, <i>c</i> – <i>t</i>	2.3	?	2.50	2.26	2.00	1.90	2.09	1.99	2.01
Formic acid, <i>trans</i> – <i>cis</i>	3.90	± 0.09	6.13	5.90	4.94	4.79	4.58	4.44	4.58
Glyoxylic acid, [O=CC=O <i>t</i> , O=COH <i>c</i>] – [O=CC=O <i>t</i> , O=COH <i>t</i>]	1.2	± 0.5	–0.19	0.47	0.54	0.35	1.08	0.88	0.92
Methyl formate, <i>trans</i> – <i>cis</i>	4.75	± 0.19	6.25	6.34	5.74	5.65	5.26	5.17	5.56
Methyl acetate, <i>trans</i> – <i>cis</i>	8.5	± 1	9.40	8.83	8.34	8.21	7.75	7.62	7.84
Ethyl formate, [O=COC <i>c</i> , COCC <i>g</i>] – [O=COC <i>c</i> , COCC <i>a</i>]	0.19	± 0.06	0.49	–0.04	0.22	0.34	0.14	0.25	0.48
Propionaldehyde, <i>skew</i> – <i>cis</i>	0.67	± 0.03	1.14	1.39	0.84	0.84	0.94	0.94	0.79
2-Butanone, <i>skew</i> – <i>cis</i>	1.07	± 0.10	1.50	1.50	0.85	0.98	1.07	1.21	1.07
1,3-Butadiene, <i>g</i> – <i>s-trans</i>	2.89	?	3.04	2.68	2.47	2.39	2.94	2.86	2.54
2-Methyl-1,3-butadiene, <i>gauche</i> – <i>s-trans</i>	2.65	?	2.37	2.29	2.33	2.20	2.80	2.67	2.45
Acrolein, <i>cis</i> – <i>trans</i>	1.70	± 0.04	1.66	1.47	2.12	2.03	2.02	1.93	1.87
1,2-Difluoroethane, <i>a</i> – <i>g</i>	0.56	± 0.1	–0.45	0.21	0.68	0.58	0.53	0.43	0.67
1,2-Dichloroethane, <i>g</i> – <i>a</i>	1.08	± 0.10	1.91	1.52	1.29	1.29	1.57	1.57	1.49
1-Fluoropropane, <i>a</i> – <i>g</i>	0.35	± 0.03	0.28	0.60	0.05	0.03	0.14	0.12	0.21
1-Chloropropane, <i>a</i> – <i>g</i>	0.09	± 0.02	–0.37	–0.10	0.01	–0.03	–0.08	–0.12	–0.10
2-Methoxytetrahydropyran, [OCOMe <i>g</i> , OMe eq] – [OCOMe <i>g</i> , OMe ax]	1.05	?	1.47	2.29	1.49	1.30	1.42	1.24	1.45
2,5-Dimethyl-1,3-dioxane, [2 eq, 5 ax] – [2 eq, 5 eq]	0.92	± 0.01	0.61	–0.14	0.47	0.63	0.61	0.77	0.85
Isopropylamine, lpNCH <i>gauche</i> – <i>anti</i>	0.45	?	0.33	0.21	0.54	0.50	0.36	0.33	0.37
Cyclohexylamine, ax – eq	1.15	?	0.70	0.11	0.56	0.69	0.63	0.75	0.92
Piperidine, ax – eq	0.53	± 0.13	0.82	0.60	0.87	0.78	0.77	0.69	0.82
<i>N</i> -Methylpiperidine, ax – eq	3.15	± 0.1	3.60	3.33	3.65	3.58	3.69	3.62	3.54
Ethanol, <i>gauche</i> – <i>anti</i>	0.12	± 0.01	0.11	–0.08	–0.02	–0.06	0.06	0.03	0.19
Isopropanol, HCOH <i>a</i> – <i>g</i>	0.28	?	0.22	0.16	0.23	0.20	0.24	0.20	0.34
Cyclohexanol, ax C ₁ – eq C ₁	0.58	± 0.02	0.25	–0.35	0.26	0.33	0.44	0.51	0.47
Methyl ethyl ether, <i>g</i> – <i>a</i>	1.5	± 0.2	1.67	1.39	1.45	1.41	1.38	1.34	1.51
Methyl vinyl ether, C=COC <i>skew</i> – <i>cis</i>	1.70	± 0.09	1.98	2.89	2.68	2.27	2.64	2.23	2.14
Diethyl ether, [CCOC <i>a</i> , COCC <i>g</i>] – [CCOC <i>a</i> , COCC <i>a</i>]	1.14	± 0.05	1.66	1.35	1.49	1.48	1.36	1.34	1.52
Methoxycyclohexane, ax C ₁ – eq C ₁	0.55	± 0.02	0.22	–0.70	–0.21	–0.01	0.07	0.28	0.33
Butane, <i>gauche</i> – <i>anti</i>	0.67	± 0.05	0.95	0.68	0.61	0.65	0.62	0.66	0.72
Cyclohexane, twist boat – chair	5.5	?	6.76	6.63	6.22	6.14	6.15	6.07	5.64
Methylcyclohexane, ax – eq	1.75	± 0.05	2.30	1.90	1.64	1.69	1.69	1.74	1.80
2,3-Dimethylbutane, HC ₂ C ₃ H <i>gauche</i> – <i>anti</i>	0.05	± 0.03	–0.10	0.04	0.08	0.04	0.03	–0.01	–0.02

perfect agreement as a theoretical model based on potential-energy differences can come, given that enthalpy, free energy, and solution contributions to the measured experimental differences are not always negligible.³¹ Force-field conformational energies computed from potential-energy differences should not do much better than this in reproducing experiment, but can be taken to reflect error to the extent that they do more poorly. In comparison, the HF/6-31G* model (0.72 kcal/mol RMSD) is significantly less accurate; adding MP2 electron correlation corrections to the small 6-31G* basis set (0.70 kcal/mol RMSD) leads to little improvement. A force field that was parameterized to fit to either of these lower level theoretical models could therefore have difficulty matching the performance of one like MMFF94 or MMFF94s that was fit to higher quality *ab initio* data.

COMPARISON OF FORCE-FIELD RESULTS TO EXPERIMENT

Tables I and II compare force-field conformational energy differences to experimental results. All instances in which the force-field value differs from experiment by more than 1.5 kcal/mol are shown in boldface, while differences exceeding 3 kcal/mol are shown in bold underline. Each comparison has been defined to make the experimental difference positive. Consequently, negative force-field values correspond to qualitatively incorrect predictions.

Tables V and VI summarize Tables I and II by listing RMSD and maximum deviations, the numbers of qualitatively incorrect (wrong sign) predictions, and the numbers of deviations lying in specified error ranges. Also shown in Table V are the numbers of cases in which no conformational en-

TABLE III.
(Continued)

Conf. Comparison	Expt. ^b	Delta	HF / 6-31G*	MP2 / 6-31G*	MP2 / TZP	“MP4 / TZP”	LMP2 ^c	“LMP4” ^c	GVB- LMP2 ^c
Cyclooctane, <i>D</i> _{4d} -C _s boat chair	1.9	± 0.2	<u>0.53</u>	2.14	2.54	2.00	1.82	1.28	1.21
Cyclononane, [255] C ₂ – [333] <i>D</i> ₃	1.0	?	0.08	1.10	1.32	0.99	1.05	0.72	0.78
1-Butene, <i>cis</i> – <i>skew</i>	0.22	± 0.02	0.69	0.49	0.37	0.26	0.36	0.25	0.30
2-Butene, <i>cis</i> – <i>trans</i>	1.2	± 0.1	1.60	1.54	1.31	1.27	1.20	1.16	1.45

^a Values in boldface differ from experiment by > 0.5 kcal / mol; values in bold underline differ by > 1.0 kcal / mol.
^b cf. Table I.
^c With the cc-pVTZ(-f) basis set.

TABLE IV.
Summary Comparison of Theoretical Methods Versus Experiment.

Quantity	HF / 6-31G*	MP2 / 6-31G*	MP2 / TZP	“MP4SDQ / TZP”	LMP2 / cc- pVTZ(-f)	“LMP4 / cc- pVTZ(-f)”	GVB- LMP2 / cc- pVTZ(-f)
No. favoring wrong conformer ^a	4	6	2	3	1	2	2
RMSD vs. expt (kcal / mol)	0.72	0.70	0.45	0.38	0.35	0.32	0.32
Max deviation (kcal / mol)	2.23	2.00	1.04	0.90	0.92	0.88	0.81
No. deviations							
0.5–1.0 kcal / mol	5	3	8	7	7	5	4
> 1.0 kcal / mol	6	8	1	0	0	0	0

The HF / 6-31G* calculations used HF / 6-31G*-optimized geometries; all others used MP2(FULL) / 6-31G*-optimized geometries. See text for definitions of the composite MP4SDQ / TZP and LMP4 / cc-pVTZ(-f) models.
^a The number of cases in which the *ab initio* and experimental determinations disagree as to which conformer is lower in energy.

TABLE V.
Summary of Comparisons of Conformational Energies Versus Experiment and *Ab Initio* Data (Set 1).

Quantity	MMFF 94	MMFF 94s	CFF 95	CVFF	MSI CHARMm	AMBER*	OPLS*	MM2*	MM3*
No. conformational comparisons	37	37	37	34	36	37	37	37	37
No. <i>ab initio</i> conformers having no local force-field minimum	0	0	0	3	1	0	0	0	0
No. favoring wrong conformer	1	1	5	13	4	8	9	3	3
RMSD vs. Expt	0.37	0.38	1.06	2.36	0.78	1.29	1.68	1.75	0.72
Max deviation	0.99	0.99	4.80	6.11	2.07	4.60	5.64	7.47	2.57
RMSD vs. "MP4SDQ / TZP"	0.33	0.33	1.17	2.35	0.73	1.37	1.79	1.62	0.79
RMSD vs. GVB-LPM2 / cc-pVTZ(-f)	0.28	0.27	1.13	2.32	0.72	1.35	1.70	1.62	0.76
No. deviations									
1–2 kcal / mol	0	0	4	14	4	7	6	2	4
2–3 kcal / mol	0	0	1	3	2	1	0	0	1
3–5 kcal / mol	0	0	1	4	0	2	4	0	0
5–7 kcal / mol	0	0	0	3	0	0	1	1	0
7–10 kcal / mol	0	0	0	0	0	0	0	1	0

This table summarizes the detailed results in Table I. All energy quantities are in kilocalories / mole. The number of possible conformational comparisons is 37. The *ab initio* reference conformational energies are the MP4SDQ / TZP or GVB-LMP2 / cc-pVTZ(-f) results shown in Table III.

ergy could be calculated because the force field failed to give a local minimum corresponding to one of the two reference MP2/6-31G* conformers; no such instances arose for set 2. This table also reports RMSDs from the reference "MP4SDQ / TZP" and GVB-LMP2/cc-pVTZ(-f) conformational energies listed in Table III.

For set 1 (Table I), all force fields except MMFF94 and MMFF94s make at least two errors of 1.5 kcal/mol or more, and most make at least one

error of 3 kcal/mol or greater. In particular, CVFF makes seven such errors and OPLS* makes five, though MM2* incurs the largest individual error (7.47 kcal/mol). As Table V shows, MM3* and MSI CHARMm fare next best, but make errors roughly twice as large as those made by MMFF94 and MMFF94s. For set 2 (Tables II, VI), in contrast, four force fields [MM2*, MSI CHARMm, MMFF94 (identical to MMFF94s for these systems), and MM3*] perform comparably. Here, however, the

TABLE VI.
Summary of Comparisons of Conformational Energies Versus Experiment (Set 2).

Quantity	MMFF 94 / 94s	CFF 95	CVFF	MSI CHARMm	AMBER*	OPLS*	MM2*	MM3*
No. favoring wrong conformer	4	7	7	4	5	7	2	2
RMSD vs. expt	0.74	2.21	2.86	0.70	1.03	1.28	0.68	0.78
Max deviation	1.45	4.24	5.78	1.66	1.69	2.91	1.87	2.27
No. deviations								
1–2 kcal / mol	4	5	7	3	9	4	3	2
2–3 kcal / mol	0	1	4	0	0	3	0	1
3–5 kcal / mol	0	6	4	0	0	0	0	0
5–7 kcal / mol	0	0	1	0	0	0	0	0

This table summarizes the detailed results in Table II. All energy quantities are in kilocalories / mole. The number of conformational comparisons is 19 for all force fields.

RMSDs are about twice those found for MMFF94 and MMFF94s for set 1. The poorer results for MMFF94 largely arise from a systematic error that affects the halocyclohexanes that dominate the test set. In particular, MMFF94's torsional parameterization overly stabilizes axial halogen substituents. This is a flaw that should be addressed in any future torsional reparameterization. The predominance of halides in set 2 also works to the disadvantage of CFF95 (2.21 kcal/mol RMSD), which performs almost as poorly as CVFF (2.86 kcal/mol RMSD).

In assessing the performance of the force fields, it is well to keep in mind that none was specifically parameterized for all the systems included in sets 1 and 2. CFF95, for example, makes relatively large errors for glyoxylic acid and methyl vinyl ether, compounds that contain moieties for which it has torsional parameters when taken in isolation but not in combination.³² The poor results for 1,2-difluoroethane in Table I and for the halides in Table II also result from a lack of specific parameters. As noted in the previous paragraph, even MMFF94 and MMFF94s suffer from underparameterization to some degree in that their derivation failed to consider axial/equatorial differences in halocyclohexanes.

We did not attempt to determine which systems lie within the specific parameterization of the various force fields. Indeed, it is not always possible to do so. For CFF95 and CVFF, for example, the version of Cerius² we used (Version 3.0) did not allow the user to determine when low-level parameters are being assigned. In the case of CFF95, however, the developers of the force field, at our request, used the alternative (and original) implementation in DISCOVER⁹ to determine that the comparisons for glyoxylic acid, acrolein, 1,2-difluoroethane, 1,2-dichloropropane, 1-fluoropropane, 1-chloropropane, and methyl vinyl ether all require default parameters. In addition, they advise that the version of CFF95 that we tested is one that did not yet allow the central C—C bonds in 1,3-butadiene and 2-methyl-1,3-butadiene to be properly treated as delocalized single bonds (as opposed to full double bonds).³² When these nine cases are omitted, the RMSD and maximum deviations for CFF95 fall from 1.06 and 4.80 kcal/mol to 0.54 and 1.58 kcal/mol, respectively, about 50% higher than those of 0.36 and 0.99 kcal/mol for MMFF94 for the same 28 comparisons.

As this example illustrates, larger errors can sometimes be understood as resulting from a lack of specific parameterization. Ultimately, however,

software packages that allow calculations like those reported in Tables I, II, and SM-I (discussed below) to go forward must take responsibility for the results. It is not sufficient to say that a given force field performs well within its domain of specific parameterization if that domain is not sufficiently extensive to support realistic applications. For this reason, the reader who wishes to make an optimal choice of force field should perhaps examine the conformational-energy comparisons presented in this article and the accompanying Supplementary Material to determine whether errors made by a given force field are or are not likely to be relevant to the work he or she intends to do.

To be sure, other sets of conformational energies could be constructed that would require MMFF94 and MMFF94s to rely on empirical-rule or default parameters and would cast them in less favorable light. For example, CFF95 describes hydrazines (for which it is specifically parameterized) much more accurately than does MMFF93³² (or than would MMFF94). It would be useful to develop consensus sets of broadly based test systems that accurately reflect the combinations of chemical moieties likely to be encountered in pharmaceutical or other bioorganic applications. Such sets could then be used to impartially evaluate biomolecular force fields. Lacking such consensus test sets, however, we chose to use data we had available in the hope that the results would provide useful guidance to users of modeling software. The same issue arises later in the article for intermolecular-interaction energies and geometries, where guidance is particularly needed because no general survey appears to have yet been published.

Comparisons to *ab initio* Theory for Conformational Energies

In this section we extend the conformational-energy comparisons to a much wider range of chemical systems. The reference data consist of 147 "MP4SDQ/TZP" energy differences between equilibrium conformers taken from table I of ref. 4. Table SM-I (Supplementary Material)²³ gives the detailed comparisons and Table VII summarizes the results. That this level of theory is suitable for characterizing molecular force fields is demonstrated by the results in Table V, which show that the conformational comparisons of set 1 give similar RMSDs versus experiment, "MP4SDQ/TZP"

TABLE VII.
Summary of Comparisons of Conformational Energies Versus “MP4SDQ / TZP” Data.

Quantity	MMFF 94	MMFF 94s	CFF 95	MSI CHARMm	AMBER*	OPLS*	MM2*	MM3*
No. conformational comparisons ^a	146	142	139	140	136	139	140	129
No. lacking parameters	0	0	0	0	0	0	0	12
No. <i>ab initio</i> conformers having no local force field min	1	5	8	7	11	8	7	6
No. favoring wrong conformer	7	8	32	31	38	32	30	22
RMSD	0.32	0.33	1.33	1.66	1.85	3.72	1.99	1.08
Max deviation	1.56	1.56	5.37	6.24	11.55	20.45	11.07	3.96
No. deviations								
1–2 kcal / mol	2	2	21	23	26	22	14	25
2–3 kcal / mol	0	0	13	11	13	7	1	6
3–5 kcal / mol	0	0	5	6	4	5	13	3
5–7 kcal/mol	0	0	1	5	4	4	3	0
7–10 kcal / mol	0	0	0	0	0	5	1	0
> 10 kcal / mol	0	0	0	0	1	6	1	0

^a The number of possible conformational comparisons is 147. Detailed results are given in Table SM-I (Supplementary Material).²³

calculation, and GVB-LMP2/cc-pVTZ(-f) calculation for each of the force fields tested.

All calculations were again carried out with a constant (default) dielectric of 1.0 and used no cutoffs on intermolecular interactions; all force-field optimizations were started from the reference MP2/6-31G* geometry. Apart from two illustrative systems discussed below, we excluded the CVFF force field from this part of the study because its poor performance for the conformational energies examined in the previous section did not justify the extensive manual effort that would have been required to collect the data.

As can be seen from Table VII, MMFF94 and MMFF94s show RMSDs that only slightly exceed 0.3 kcal/mol and are never in error by more than 1.6 kcal/mol. This good performance reflects the fact that each was accurately parameterized to fit this (and other) data and is sufficiently flexible to do so, though we again point out that the bifunctional compounds in the data set typically yield the largest errors in conformational energy.⁴

The seven other force fields performed more poorly. The least accurate is OPLS*, which shows the largest RMS error (3.72 kcal/mol) and makes errors in conformational energy that reach 20 kcal/mol for ethylenediamine. For this case, OPLS* finds the N—C—C—N gauche conformation to be greatly overstabilized, relative to N—C—C—N

trans, by an internal N—H···N hydrogen bond (cf. Table SM-I). The end result is that the gauche conformer distorts to cis planar and closes its non-bonded N—H···N distance to a physically unreasonable 1.10 Å! The lack of van der Waals (vdW) repulsion for the polar NH proton may be the factor that precipitates this collapse. AMBER*, whose error for ethylenediamine exceeds 11 kcal/mol, suffers the same fate but to a lesser degree. Both force fields also yield a too highly stabilized cis planar (instead of gauche) internally hydrogen-bonded structure for ethylene glycol and fail to yield local minima for two other non-hydrogen-bonded O—C—C—O gauche conformers found on the MP2/6-31G* surface (Table SM-I).

MM3* (1.08 kcal/mol RMSD) fares best among the remaining five force fields. However, it recognizes the smallest range of chemistry and lacks parameters for a dozen of the systems examined. MM2* (1.99 kcal/mol RMSD) is more widely parameterized but makes significantly larger errors. The good performance that Gundertofte et al. found for MM2* for conformational energies using a distance-dependent dielectric model¹⁴ was not sustained for the present data.

CFF95, the next best force field after MM3*, makes RMSD and maximum deviations (1.33 and 5.37 kcal/mol, respectively) that are about 4 times larger than those found for MMFF94 and MMFF

94s. Some of the difference is undoubtedly attributable to the fact that the MMFF force fields were trained on this data while CFF95 was not. Part also arises because CFF95 in some cases relies on default or constructed values for key atomic charge and torsion parameters. However, part of the difference may reflect the intrinsic limitation that must arise because CFF95's parameterization used relatively inaccurate HF/6-31G* conformational energies that in turn limit the accuracy obtainable in the derived force field (see the discussion in the preceding section).

The assignment of nonzero charges to aliphatic hydrogens appears to be an issue for several of the force fields. Using the four conformers of cyclohexanol as a test case, we argued previously⁴ that MMFF, which assigns zero charge to such hydrogens, could not accurately fit the *ab initio* conformational energies if its aliphatic hydrogens carried appreciable positive charges. The problem arises because the equatorial- and axial-*C_s* conformers, in which the hydroxyl hydrogen folds back over the ring, are significantly stabilized relative to the *C₁*

conformers by dominant electrostatic interactions with the negatively charged ring carbons. As a result, even if other force-field terms, such as vdW interactions and angle-bending deformations, oppose the electrostatic term, the axial-*C_s* conformer improperly becomes the most stable as the hydrogen charge increases.³³ By comparing the numbers of gauche and anti H—O—C—C and O—C—C—C torsion interactions, we further argued that MMFF's torsional parameters could not compensate for sizable contributions from such an electrostatic stabilization without damaging other conformational comparisons. However, we could not say whether a force field such as CFF95 that employs a broad selection of cross terms might be able to provide the needed compensation in some other way.

To show how force fields that employ positively charged aliphatic hydrogens fare for such systems, we present conformational and total electrostatic energies for cyclohexanol and cyclopentanol in Table VIII for CFF95, CVFF, MSI CHARMM, AMBER*, and CHARMM 22,³⁴ as well as for MMFF94

TABLE VIII.
Influence of Aliphatic Hydrogen Charges on Conformational Energies for Cyclohexanol and Cyclopentanol.

Method	<i>q_{HC}</i>	Total Conformational Energy				Electrostatic Energy			
		OH07a	OH07b	OH07c	OH07d	OH07a	OH07b	OH07c	OH07d
GVB-LMP2 / cc-pVTZ(-f)	—	0.28	1.37	0.00	0.47	—	—	—	—
“MP4SDQ / TZP”	—	0.18	1.14	0.00	0.33	—	—	—	—
MMFF94 / 94s	0.000	0.20	1.01	0.00	0.32	0.	0.	0.	0.
CFF95	0.053	0.14	−0.49	0.00	0.24	−8.28	−8.66	−7.84	−6.86
CVFF	0.100	−0.98	−0.75	0.00	— ^a	−11.98	−12.50	−11.14	— ^a
MSI CHARMM	0.050	0.06	0.58	0.00	0.40	−1.72	−3.50	−1.97	−3.29
CHARMM 22	0.090	0.58	0.91	0.00	2.78	−14.75	−14.87	−13.66	−11.24
AMBER*	0.038	0.15	−0.83	0.00	−0.58	−1.33	−2.67	−1.47	−2.28

Method	<i>q_{HC}</i>	Total Conformational Energy				Electrostatic Energy			
		OH06a	OH06b	OH06c	OH06d	OH06a	OH06b	OH06c	OH06d
GVB-LMP2 / cc-pVTZ(-f)	—	0.99	1.00	0.76	0.00	—	—	—	—
“MP4SDQ / TZP”	—	1.11	1.05	1.14	0.00	—	—	—	—
MMFF94 / 94s	0.000	0.82	0.60	0.47	0.00	0.	0.	0.	0.
CFF95	0.053	−0.27	−0.33	−0.53	0.00	−8.23	−9.00	−7.93	−7.20
CVFF	0.100	0.22	0.07	1.04	0.00	−13.24	−14.19	−12.56	−14.08
MSI CHARMM	0.050	— ^b	−0.94	−0.62	0.00	— ^b	−3.95	−2.62	−3.56
CHARMM 22	0.090	−0.83	−1.52	−1.85	0.00	−14.84	−15.86	−13.95	−12.08
AMBER*	0.038	— ^b	−0.36	0.70	0.00	— ^b	−3.13	−2.01	−2.74

Energies are in kilocalories / mole.
^a MP2 / 6-31G* starting geometry collapses to OH07b upon optimization.
^b MP2 / 6-31G* starting geometry collapses to OH06b upon optimization.

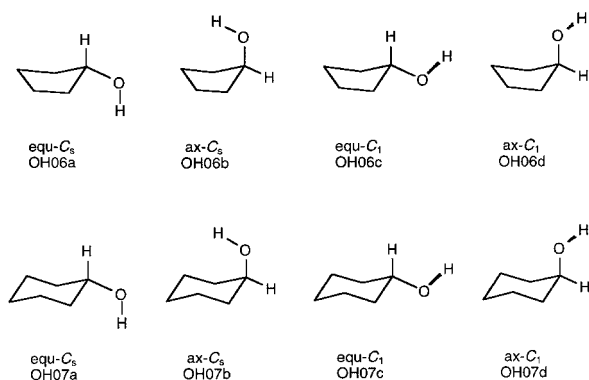


FIGURE 1. Equatorial and axial conformers of cyclopentanol (OH06a-d) and cyclohexanol (OH07a-d).

(which is identical to MMFF94s for these systems). The reference *ab initio* energies were obtained at the “MP4SDQ/TZP” and GVB-LMP2/cc-pVTZ(-f) levels. Geometries are shown in Figure 1.

Table VIII shows that CFF95 ($q_{\text{HC}} = 0.053$) and AMBER* ($q_{\text{HC}} = 0.038$) indeed predict the axial- C_s conformer for cyclohexanol (OH07b) to be the most stable, whereas *ab initio* calculation finds it to be the least stable. CVFF ($q_{\text{HC}} = 0.010$) also wrongly favors the electrostatically stabilized C_s conformers OH07a and OH07b. The electrostatic interaction is strong enough in this case to pull the hydroxyl hydrogen of axial- C_1 OH07d back over the ring, thereby converting the starting MP2/6-31G* geometry into axial- C_s OH07b and leaving no axial- C_1 minimum. Surprisingly, MSI CHARMM ($q_{\text{HC}} = 0.050$) reproduces the *ab initio* relative energies for cyclohexanol quite well, despite the fact that the axial- C_s conformer is favored electrostatically. The full set of energy components (not shown) indicate that a selective disfavoring of the all-gauche H—O—C—C and O—C—C—C torsion interactions of OH07b, the axial- C_s conformer, plays a key role. The same MSI CHARMM torsional parameters, however, fail to yield a local minimum for the equatorial- C_s conformer of cyclopentanol (OH06a), which distorts to axial- C_s OH06b, and yield relative energies for the remaining three conformers that are in complete disagreement with the *ab initio* data. CHARMM 22 ($q_{\text{HC}} = 0.09$) also shows reasonable conformational energies for axial- and equatorial- C_s OH07a and OH07b relative to equatorial- C_1 OH07c, even though the first two are more highly stabilized electrostatically. However, the conformational energy of axial- C_1 OH07d is too high, and the same torsion parameters (which in a departure from the usual practice include one-, two-, and three-fold compo-

nents for the H—O—C—C interaction³⁵) give completely erroneous conformational energies for cyclopentanol. With the possible exception of CVFF (which, as noted, performs poorly for cyclohexanol), each of the other force fields that uses positively charged aliphatic hydrogens also behaves qualitatively incorrectly for cyclopentanol.

In sum, only MMFF94 yields conformational energies for both cyclohexanol and cyclopentanol that are in reasonable accord with the *ab initio* data. Thus, our challenge⁴ still stands: it remains to be demonstrated that a force field that uses appreciable positive charges for aliphatic hydrogens can successfully reproduce conformational energies in systems such as these. This is a challenge that future force-field developers should take to heart if they wish to avoid undercutting their efforts at the outset.

Comparisons to Theory for Intermolecular Interactions

This section examines the ability of the force-field models to reproduce values and trends in scaled quantum mechanical (SQM) hydrogen-bonding interaction energies and geometries. Figure 1 of ref. 2 shows the relative orientation of the monomers in the 66 hydrogen-bonded complexes we consider. Full listings of the calculated interaction energies, heteroatom distances, and hydrogen-bond angles are given in the Supplementary Material²³; the results are summarized in Table IX. For explicit comparison, however, we focus on the smaller set of complexes listed in Table X. These complexes have been grouped into sets of related structures so that physical theory and general knowledge can be used to assess the reasonableness of the calculated interaction energies. In addition to the results to be reported for the seven force fields considered in detail in previous sections, we also present partial results for CHARMM 22,³⁴ whose parameterization (with modest extension³⁶) is sufficient to allow it to be applied to about half of the full set of complexes. As the footnote to Table IX indicates, each of the other force fields except MM3* is able to handle all or nearly all of the dimers. As before, all calculations used a unit constant dielectric and avoided cutoffs on nonbonded interactions. All force-field geometry optimizations began from the geometry of the reference *ab initio* optimized monomer or dimer;

TABLE IX.
Summary of Hydrogen-Bonding Comparisons to Scaled HF / 6-31G* Data.

Force Field ^a	Interaction Energy (kcal / mol)			X ... Z Distance (Å)		X—H ... Z Angle RMSD
	RMSD	Ave Dev	Max Dev	RMSD	Ave Dev	
MMFF94	0.77	−0.25	2.52	0.09	0.02	14.6°
MMFF94s	0.76	−0.24	2.52	0.10	0.03	18.1°
CFF95	2.33	1.10	6.53	0.33	0.21	27.0°
CVFF	4.36	2.24	16.39	0.41	0.23	26.1°
MSI CHARMM	3.03	0.60	13.54	0.30	0.08	34.0°
CHARMM 22	1.11	0.00	3.04	0.12	0.05	15.0°
OPLS*	2.00	−0.49	6.61	0.21	0.02	22.9°
AMBER*	1.60	0.08	6.06	0.19	0.04	26.9°
MM2*	3.86	1.92	7.53	0.26	0.06	39.5°
MM3*	3.81	2.12	13.31	0.50	0.22	34.0°

^a Each of the force fields handles all 66 hydrogen-bonded dimers except for CVFF, for which the Cerius² implementation could not perform the atom typing for imidazole; MM3*, which lacks parameters for 12 of the dimers; and CHARMM 22, which even with extensions made locally³⁶ lacked parameters for about half the systems.

restrained optimizations were employed in a few cases to locate elusive stationary points.³⁷

SQM DATA

The SQM interaction energies were obtained by increasing the raw HF/6-31G* values (not counterpoise corrected) by 15% for the water dimer and by 10% for other interactions between uncharged monomers, while unscaled HF/6-31G* values were used for dimers involving charged monomers. The SQM interaction distances were taken as 92% of the HF/6-31G* heteroatom distances for neutral monomers and as 96% of the distances for dimers involving charged monomers. This scaling of the reference interaction energies and distances is motivated by the need to fit condensed-phase interaction energies and distances with a fixed-charge “effective potential” model. A full discussion of the basis for scaling, together with citations of precedent in the work of Karplus, Jorgensen, and coworkers, is given in ref. 2. A key element concerns the linear water dimer, for which the successful TIP3P³⁸ and SPC³⁹ water models find that a dimer interaction energy of approximately −6.5 kcal/mol (about 15% larger than the HF/6-31G* value of −5.6 kcal/mol, as MacKerell and Karplus noted⁴⁰) is needed to fit the heat of vaporization and other condensed-phase properties. In addition, these two water models find that the HF/6-31G* O...O interaction distance of 2.97 Å exceeds by ~ 8% the distance of 2.74–2.75 Å

they require to reproduce the density and other properties of liquid water.

The comparisons for water also formed the basis for the scaling of the quantum mechanical results we used in the derivation of MMFF94,² where we also followed the lead of MacKerell and Karplus.⁴⁰ However, there are some differences in detail. For example, MMFF94’s parameterization implicitly assumed equally enhanced HF/6-31G* interaction energies for the water dimer and for other neutral-monomer dimers and also assumed that an increase, albeit smaller, should apply to dimers involving a charged monomer. The use of unscaled interaction energies for dimers involving charged monomers is consistent with the practice of MacKerell and Karplus⁴⁰; the smaller scaling for neutral dimers reflects the critique of Beachy et al.,⁴¹ who challenged the notion that organic matter in aqueous solution should be as strongly polarized as is bulk water, in which cooperative effects predominate.

**FORCE-FIELD INTERACTION ENERGIES
AND GEOMETRIES**

Table IX summarizes the detailed results for the full set of 66 hydrogen-bonded complexes given in the Supplementary Material.²³ This table shows that only CHARMM 22 (which like MMFF94 was derived from fits to scaled HF/6-31G* data^{34,40}) is comparable to MMFF94 and MMFF94s in reproducing the SQM interaction energies. AMBER*,

TABLE X. Comparison of Selected Scaled-HF / 6-31G* and Force-Field^a Intermolecular Interaction Energies.

Dimer	SQM ^b	MMFF 94	MMFF 94s	CFF 95	CVFF	MSI CHARMm	AMBER*	OPLS*	MM2*	MM3*
HOH...OH ₂	-6.47	-6.61	-6.61	-5.40	-6.40	-6.83	-7.09	-6.84	-4.87	-7.11
CH ₃ OH...OHCH ₃	-6.09	-6.03	-6.03	-5.65	-5.03	-6.48	-4.73	-7.64	-4.68	-5.54
CH ₃ OH...OH ₂	-6.15	-6.14	-6.14	-6.53	-6.78	-5.19	-5.14	-7.46	-4.73	-7.80
HOH...OHCH ₃	-6.10	-6.32	-6.32	-4.61	-4.41	-6.24	-6.27	-6.78	-4.53	-5.14
C ₆ H ₅ OH...OH ₂	-8.09	-8.45	-8.45	-6.28	-7.57	-5.66	-7.54	-7.50	-3.62	-2.76
HOH...OHC ₆ H ₅	-5.16	-5.08	-5.08	-3.97	-4.18	-6.76	-5.41	-7.23	-3.46	-2.65
HOH... <i>t</i> -NMA	-8.03	-8.19	-8.25	-5.67	-6.80	-6.87	-8.75	-7.56	-6.97	-5.14
<i>t</i> -NMA...OH ₂	-5.97	-6.86	-6.87	-7.41	-4.19	-5.20	-5.57	-8.73	-5.82	-8.72
HOH...O=CHOCH ₃	-6.39	-6.84	-6.84	-4.58	-6.19	-7.47	-6.48	-5.74	-5.09	-3.97
HOH...O(CH ₃)CH=O	-3.82	-2.63	-2.63	≠ min	-3.20	-5.68	-3.43	-3.27	≠ min	≠ min
Acetic acid, cyclic	-17.10	-17.10	-17.10	-10.57	-11.14	-3.56	-11.04	-13.73	-14.51	-3.79
Formamide, cyclic	-14.78	-12.26	-12.26	-10.02	-6.53	-11.68	-15.04	-16.00	-9.63	-8.48
HOH...NH ₃	-7.22	-6.83	-6.83	-3.74	-1.98	6.39	-7.46	-7.54	-3.64	-2.69
HOH...pyridine	-6.63	-7.10	-7.10	-4.25	-3.36	-4.56	-7.13	-5.72	-3.41	-3.59
HOH...thiophene	-2.66	-2.71	-2.71	-4.36	-3.76	-4.61	-4.86	-2.91	-3.67	-2.81
HOH...imidazole	-7.77	-7.94	-7.94	-6.05	na ^c	-7.42	-6.88	-6.00	-3.04	-2.94
Imidazole...OH ₂	-7.00	-7.92	-7.92	-7.81	na ^c	-10.83	-5.55	-9.22	-2.66	-6.24
C ₆ H ₅ NH ₂ ...OH ₂	-4.62	-4.86	-4.54	-5.17	-2.82	-4.17	-7.23	-5.30	-2.91	-2.00
NH ₃ ...O(CH ₃) ₂	-3.21	-3.34	-3.34	-1.18	-1.44	-3.51	-4.33	-3.67	-2.06	-2.81
HOH...MeEtNH-O	-15.48	-14.87	-14.87	-21.09	-16.58	-12.82	-15.54	-15.56	-15.02	na
HOH...C ₅ H ₅ N-O	-10.69	-10.61	-10.61	-7.20	-3.53	-11.76	-7.78	-4.08	-4.59	na
HOH...S(CH ₃) ₂	-3.56	-3.48	-3.48	-2.05	-1.23	-1.68	-3.39	-4.54	-2.41	-2.70
HSH...OH ₂	-2.93	-2.91	-2.91	-2.19	-0.98	-2.96	-4.12	-6.58	-2.58	-6.79
HSH...SH ₂	-0.96	-1.25	-1.25	-1.23	-0.46	-2.31	-2.94	-3.52	-0.74	-0.88

^a Individual underlined values differ from the reference scaled HF / 6-31G* value by 2 kcal / mol or more; groups of values printed in boldface differ qualitatively from the SQM values (see text).

^b The SQM interaction energies increased the unscaled HF / 6-31G* interaction energies by 15% for the two water...water dimers and by 10% for water...other and other...other dimers involving neutral monomers. Although not reflected in this table, HF / 6-31G* interaction energies were used without scaling for dimers involving charged monomers.

^c Cerius² could not assign atom types for imidazole for this force field.

with errors about twice those for MMFF94, is next best, followed by OPLS* and CFF95. Finally, MSI CHARMm, MM3*, and MM2* all show RMSDs that exceed 3 kcal/mol; that for CVFF exceeds 4 kcal/mol. The average signed deviations show that interaction energies for OPLS*, MMFF94, and

MMFF94s on balance are slightly too negative. In contrast, average interaction energies for CHARMM 22 and AMBER* are on target, while those MSI CHARMm are slightly too small in magnitude. CFF95, MM2*, MM3*, and CVFF all give even smaller interaction energies that in part

account for their larger overall RMSDs. Maximum deviations range from 2.5 kcal/mol for MMFF94 and MMFF94s to 16.4 kcal/mol for CVFF.

Table IX also shows that MMFF94, MMFF94s, CHARMM 22, OPLS*, and AMBER* yield non-bonded $X\cdots Z$ heteroatom distances that closely match the average SQM distances. The two MMFF force fields (which differ for only a few of the hydrogen-bonded dimers) and CHARMM 22 show the smallest RMSDs and reproduce the scaled HF/6-31G* geometries best. At the opposite extreme, the heteroatom distances for CFF95, CVFF, and MM3* are systematically ~ 0.2 Å longer than the SQM values. These force fields produce looser interaction geometries that may be appropriate for modeling gas-phase behavior. The final column shows that MMFF94, MMFF94s, and CHARMM 22 also reproduce the $X-H\cdots Z$ hydrogen-bond angles of the dimers best; the RMS errors are typically 2–3 times larger for the other force fields.

Table X shows results for specific complexes. To highlight cases of questionable behavior, all instances in which the calculated force-field interaction energy differs from the SQM value by more than 2 kcal/mol are underlined. In addition, all instances in which we judged the interaction energies for a given set of complexes to *differ qualitatively* from the SQM values are printed in boldface. When the SQM values themselves show a clear trend, *differ qualitatively* in most cases means that the force field gives a different ordering. On the other hand, when the SQM interaction energies are comparable, this designation means that the force-field interaction energies erroneously show a large difference. Bold facing is also used to highlight instances in which no comparison could be made because the force-field model failed to yield a local minimum for one of the complexes.

All force fields except MMFF94 and MMFF94s show numerous qualitative and quantitative errors. For example, several give an interaction energy for the linear water dimer that appears too small in magnitude to be appropriate for aqueous-phase modeling. Moreover, many of the force fields fail to predict that water and methanol have comparable strengths as hydrogen-bond donors and acceptors. Indeed, some even fail to recognize that phenol (a weak acid) is a stronger hydrogen-bond donor but weaker hydrogen-bond acceptor than water, though this is a matter of common knowledge.

The fact that CFF95, OPLS*, and MM3* find *trans*-*N*-methylacetamide to be a stronger hydrogen-bond donor than acceptor points up an imbal-

ance in their parameterization that is of particular importance for biomolecular modeling. In the case of methyl acetate, the force fields generally recognize that the doubly bonded carbonyl oxygen is a stronger hydrogen-bond acceptor than is the divalent "ester" oxygen. For CFF95, MM2*, and MM3*, however, no local minimum could be found for the latter complex. The force-field interaction energies are especially unsatisfactory for the cyclic acetic acid and formamide dimers. Indeed, CFF95, MSI CHARMM, AMBER*, and MM3* make their largest individual errors for the acetic acid dimer, while MMFF94 and MMFF94s make their largest errors for the formamide dimer.

CFF95, CVFF, MSI CHARMM, MM2*, and MM3* yield especially troubling results for the dimers involving ammonia, pyridine, and thiophene as hydrogen-bond acceptors. In line with chemical intuition, the SQM interaction energies and the physical data show that ammonia (pK_b 9.24) is a somewhat stronger base in aqueous solution than pyridine (pK_b 8.8),⁴² whereas thiophene is not appreciably basic. Nevertheless, CFF95 incorrectly makes thiophene the strongest base (hydrogen-bond acceptor) and ammonia the weakest. This and other discrepancies in relative interaction energies may result from the fact that the CFF force fields combine charge parameters determined in a variety of ways from different and somewhat incommensurate kinds of data.² The comparisons presented here show that the resultant charge set is not able to describe general intermolecular interactions in a balanced manner.

Finally, we note that a number of force fields poorly describe the relative and/or absolute strengths of imidazole, a basic biomolecular building block, as a hydrogen-bond acceptor and donor; that some fail to recognize that aniline is a stronger hydrogen-bond donor than ammonia; and that many "handle" aromatic and aliphatic N-oxides but produce highly inaccurate results.

In summary, apart from MMFF94 and MMFF94s, all force fields for which detailed results are given in Table X show serious deficiencies in describing intermolecular interactions. In particular, few seem appropriate for use in aqueous-phase simulations. One can, of course, question the choice of HF/6-31G* as the theoretical model (although we previously described unsuccessful attempts to find a better one²) and/or the scaling protocol applied to the quantum mechanical data. It should be noted, however, that force fields that poorly reproduce the SQM data also poorly reproduce the

unscaled data, which MMFF94, MMFF94s, and CHARMM 22 again describe best (Table XI).

To be sure, “good” interaction energies are not sufficient to ensure success in biomolecular modeling applications. For example, evidence from condensed-phase simulations is accumulating that MMFF94’s vdW parameterization needs to be revised,^{43–45} as indeed it is being.⁴⁶ In contrast, force fields such as OPLS-AA,²² AMBER 4,²⁰ and CHARMM 22³⁴ have already achieved good success in reproducing condensed-phase results for quantities such as free energies of hydration and geometries of hydrated proteins and nucleic acids. However, large deficiencies like those reflected in Tables IX–XI are surely incompatible with success in applications that critically depend on accurate modeling of interaction energies.

Concluding Discussion

This article assesses the ability of MMFF94, MMFF94s, and seven other widely available force fields (CFF95, CVFF, MSI CHARMM, AMBER*, OPLS*, MM2*, and MM3* to reproduce experimental and theoretical conformational energies and to emulate *ab initio*, values and trends for hydrogen-bonding interaction energies and geometries. Selected results are also presented for CHARMM 22. In these studies, MMFF94 and MMFF94s perform best. CFF95, the most elaborate in functional form of the force fields considered here, produces much larger conformational energy errors, although its errors for set 1 are reduced to about 50% larger than those for MMFF94 when seven

cases that required default parameters and two cases that could not be properly described by the tested version of CFF95 are excluded. Of particular concern is CFF95’s practice of combining atomic charge parameters derived in a variety of ways from different kinds of data. This practice, which we critiqued previously,² produces relative hydrogen-bonding energies that frequently contravene both *ab initio* data and chemical expectation. For example, CFF95 wrongly finds thiophene to be a stronger hydrogen-bond acceptor than either pyridine or ammonia. In addition, it finds amides to be appreciably stronger hydrogen-bond donors than acceptors, in disagreement with *ab initio* calculation, the highly regarded OPLS force field,⁴⁷ CHARMM 22, and MMFF94. These and other imbalances need to be considered when making assessments of its suitability for applications involving intermolecular interactions.

Each of the remaining force fields also experiences significant difficulty in describing conformational energies, interaction energies, or both. For example, CVFF performs particularly poorly in both domains. MM3*, though limited in its parameterization, does moderately well for conformational energies but gives intermolecular-interaction energies that are too small to be appropriate for condensed-phase simulations in high-dielectric media. MM2*, which also gives small interaction energies, gives relatively large errors in conformational energy when the now-current BatchMin default of a unit constant dielectric is used. On the other hand, AMBER*, which describes conformational energies relatively poorly, nevertheless performs moderately well for many of the intermolec-

TABLE XI.
Summary of Hydrogen-Bonding Comparisons to Unscaled HF / 6-31G* Data.^a

Force Field	Interaction Energy (kcal / mol)			X···Z Distance (Å)	
	RMSD	Ave Dev	Max Dev	RMSD	Ave Dev
MMFF94	1.03	−0.77	2.51	0.23	−0.21
MMFF94s	1.02	−0.76	2.52	0.23	−0.21
CFF95	2.06	0.55	−7.01	0.27	−0.03
CVFF	4.12	1.71	16.39	0.35	0.00
MSI CHARMM	2.80	0.05	11.99	0.36	−0.16
CHARMM 22	1.07	−0.53	2.77	0.29	−0.14
OPLS*	2.08	−1.01	6.25	0.31	−0.22
AMBER*	1.51	−0.43	4.51	0.29	−0.20
MM2*	2.35	1.32	6.64	0.32	−0.20
MM3*	3.34	1.57	11.76	0.45	−0.03

^a See the footnote to Table IX.

ular-interaction test systems. In comparison, OPLS* performs poorly in both arenas. CHARMM 22, although limited in parameterization for general organic systems, performs comparably to MMFF for intermolecular interactions, but did poorly for cyclohexanol and cyclopentanol in the one test of conformational energies we made. Finally, MSI CHARMM performs comparably to CFF95 for conformational energies but makes some very large errors for intermolecular-interaction energies.

Among the force fields we were unable to examine, we would expect authentic MM2, MM3, and MM4, like MM2* and MM3*, to show relatively small dimer interaction energies that, if suitably balanced, might be appropriate for describing gas-phase interactions, their intended domain of applicability. The recently described OPLS-AA force field,²² in contrast, would be expected to give interaction energies that are well suited for condensed-phase modeling. Expectations for OPLS-AA conformational energies, however, are harder to define, though we note that this force field, like CFF95, has been parameterized on the basis of lower level HF/6-31G* quantum mechanical data that reproduce experimental conformational energies relatively poorly (see above). On the other hand, nonbonded interactions for OPLS-AA, as for AMBER 4 and CHARMM 22, have been successfully parameterized against condensed-phase data, whereas MMFF's parameterization has not as yet addressed such data; as noted above, indications are that MMFF's vdW parameterization, in particular, needs to be refined, though in unpublished work we find that aqueous-phase (as opposed to neat-liquid) simulations show much smaller errors.

To facilitate the evaluation of other molecular force fields, we posted the quantum chemical data used in this work on the Computational Chemistry List Web site.⁴⁸ For conformational energies, these data consist of "MP4SDQ/TZP" energies and MP2/6-31G*-optimized geometries for the molecular species considered in Tables I and SM-I, together MMFF94-optimized geometries for the species in Table II. For intermolecular interactions, they consist of HF/6-31G*-optimized structures and energies for the 66 dimers and associated monomers examined in this work and a listing specifying the atoms involved in hydrogen-bonded distances and angles. We look forward to learning the results of the application of other molecular force fields to this evaluation suite.

Acknowledgments

I wish to thank all the members of the Molecular Systems Applications Group whose requests for guidance on the accuracy and applicability of force fields available at Merck led me to perform this study. I also thank Jan Labanowski of the Ohio Supercomputer Center for posting the force-field evaluation suite on the Computational Chemistry List Web site.

Supplementary Material

This material contains a survey of experimental conformational energies for set 1 (Appendix A, Table A-I) and comparisons of *ab initio* "MP4 SDQ/TZP" and calculated force-field results for 147 conformational energies (Table SM-I). Also, detailed comparisons of calculated force-field intermolecular interaction energies and geometries to scaled quantum mechanical results are presented (Tables SM-II–SM-X). For information on accessing this Supplementary Material, see the footnote on the first page of this article.

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31. Using the same set of conformational comparisons with the exception of the cyclooctane and cyclononane comparisons added here, the Friesner group showed that errors versus experiment are significantly reduced when zero point corrections [ref. 28(a)] are added. For the expanded set, however, we found that the fits for cyclooctane and cyclononane, which are already degraded by sizable post-MP2 correlation corrections (compare entries in the final three columns of Table III), are significantly worsened by MP2/6-31G*-based zero point corrections of –0.54 and –0.33 kcal/mol, respectively. As a result, while zero point corrections do reduce the RMSD for the LMP2 model to 0.31 kcal/mol, for the overall data set they actually raise the RMSDs for the “LMP4” and GVB-LMP2 models to 0.37 kcal/mol in each case.
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35. The CHARMM 22 calculations for cyclohexanol and cyclopentanol required that residue topology entries for these structures be added to the distributed July 1997 version of the top_all22_model.inp file and that H-OH1-CT1-CT2 torsional and OH1-CT1-CT2 and CT1-CT2-CT1 angle-bending parameters be added to the distributed par_all22_prot.inp file. The parameter entries were set equal to the existing H-OH1-CT1-CT3, OH1-CT1-CT3, and CT2-CT1-CT1 entries. The residue topology entries could be generated unambiguously from atom types and charges defined for other model compounds.
36. To carry out these calculations for the broadest set of complexes that lay reasonably within the defined parameterization for CHARMM 22, residue topology entries for dimethyl ether, ammonia, ammonium cation, hydrogen sulfide, and dimethyl sulfide were added to the distributed July 1997 version of the top_all22_model.inp file by modifying related topology entries that contained the requisite chemical moieties. The associated charges could be unambiguously assigned from charges defined for existing

- residue types except in the case of dimethyl sulfide, where assigned sulfur (S) and carbon (CT3) charges of -0.10 and -0.22 represent a compromise. In addition, the extension required the addition of parameters for CT3-S-CT3, CT3-OH1-CT3 (used in dimethyl ether), and HS-S-HS angle bending and for HA-CT3-S-CT3 torsion. The first and last of these were cloned from existing CT3-S-CT2 and HA-CT2-S-CT3 (identical to HA-CT3-S-CT2) parameters; the second and third, which we did not feel would seriously affect the computed interaction energies, were assigned values based on MMFF94 (i.e., for CT3-OH1-CT3 a force constant of 86.0 and an ideal angle of 107° , and for HS-S-H a force constant of 53.0 and an ideal angle of 93.4°).
37. In general, as noted in ref. 2, such techniques were needed to study the planar C_s structure for the water dimer, the bifurcated C_s structure for the ammonia dimer, and the stacked, "pancake" structure for the *N*-methylacetamide dimer.
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 44. In addition, B. L. Bush (Merck Research Laboratories) applied perturbation theory to small organic solutes such as methane, ethane, propane, and methanol, and found that MMFF94 free energies for gas to water transfer are typically too positive (too hydrophobic), indicating insufficient van der Waals attraction between hydrocarbon moieties and water. Our own studies (unpublished) of the methane dimer using very large basis sets and very high levels of electron correlation confirm that MMFF94 vdW well depths for aliphatic hydrogen and carbon are too small in magnitude and that effective MMFF94 radii are slightly too large.
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